REMARKS

Applicants thank the Examiner for the review of the instant application. Claims 6-17 remain pending and are presented for further examination. For the reasons stated below, Applicants respectfully traverse the rejection of the pending claims.

Status of the Claims

In response to the final Office Action mailed January 9, 2006, Applicants filed an Amendment After Final Office Action on March 7, 2006. This amendment canceled Claims 4 and 5, amended Claim 12 to change the dependency from canceled Claim 4 to Claim 6. and corrected an inadvertent error in the ATCC number.

Although Applicants have not received any communication from the Examiner regarding this After-final Amendment, Applicants assume that the claim amendments have been entered, and that the current claims read as set forth in the "Listing of the Claims" section which begins on page 2 of this paper.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of Claims 6-17 under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Actions. The PTO asserts that one skilled in the art would not know how to use the claimed invention. According to the PTO, "the specification provides data showing an increase in message- in one kidney tumor tissue. However, there is no evidence regarding whether or not PRO1268 polypeptide levels are also increased." Office Action at 3. The PTO relies on Pennica *et al.,* Haynes *et al.*, and Hu *et al.,* for the propositions that the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels and that what is often seen is a lack of correlation between DNA expression and increased peptide levels. Office Action at 3. The PTO argues that further research is required to determine whether the PRO1268 polypeptide is differentially expressed, making the asserted utility not substantial.

Applicants have previously set forth the legal standard for utility. It is established that the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants first offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly kidney tumors. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1268 polypeptide is expressed at least two-fold higher in kidney tumor tissue compared to normal kidney tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the mRNA for the PRO1268 polypeptide is differentially expressed in kidney tumor tissue compared to normal kidney tissue, it is more likely than not that the PRO1268 polypeptide is likewise differentially expressed in these tumors; the PRO1268 polypeptide is therefore useful as a diagnostic tool to distinguish kidney tumor tissue from normal kidney tissue.

Applicants understand the PTO to be asserting that "one skilled in the art would view the instant expression data as merely preliminary with regard to whether or not mRNA or protein

levels of PRO1268 are specifically increased in kidney tumor. Further research would have to be done in order to determine if PRO1268 mRNA and protein are amplified, and, if so, whether or not the expression is significant enough to reasonably confirm the usefulness of PRO1268 protein as a cancer marker." Office Action at 7.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." *M.P.E.P.* § 2107.02 III B. The references cited by the PTO in support of its rejections are either irrelevant, not contrary to Applicants' arguments, or actually offer support for Applicants' position. Even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1268 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants remind the PTO of the level of evidence required to support a substantial utility.

> [T]he Appellant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the Appellant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (emphasis in original, citations omitted).

The Court of Appeals for the Federal Circuit has stated that the standard for satisfying the utility requirement is a low one:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *See Brenner v. Manson,* 383 U.S. 519, 534, 86 S.Ct. 1033, 16 L.Ed.2d 69 (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.,* 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the

> claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger,* 120 F. 274, 275 (7th Cir.1903) (test for utility is whether invention "is incapable of serving any beneficial end"). *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q. 2d 1700 (Fed. Cir. 1999) (emphasis added).

The low threshold for satisfying the utility requirement is reflected in the standard set by the Federal Circuit for invalidating a patent based on a lack of utility: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility. Some degree of utility is sufficient for patentability. Further, the defense of non-utility cannot be sustained without proof of total incapacity." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 U.S.P.Q. 473 (Fed. Cir. 1984) (emphasis added, citations omitted).

Because the standard for satisfying the utility requirement is so low, requiring total incapacity for a finding of no utility, the M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been *rarely* sustained by federal courts. Generally speaking, in these *rare* cases, the 35 U.S.C. 101 rejection was sustained [] because the Appellant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967) (underline emphasis in original, italic emphasis added).

In *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), the court held that crude screens for pharmacological activity which were reported as qualitative results without statistical analysis were sufficient to establish utility. The Appellants in *Nelson* relied on two tests to prove practical utility for derivatives of naturally occurring prostaglandins: an *in vivo* rat blood pressure (BP) test and an *in vitro* gerbil colon smooth muscle stimulation (GC-SMS) test. In the BP test, responses to the compounds were categorized qualitatively, as either a depressor (lowering) effect or a pressor (elevating) effect. *Nelson*, 626 F.2d at 854-55. In the GC-SMS test a section of colon was excised from a freshly-killed gerbil for suspension in a physiological solution, and a lever arm was connected to the colon in such a way that any contraction was recorded as a polygraph trace. *Id.* The Board held that Nelson had not shown adequate proof of practical utility, characterizing the tests as "rough screens, uncorrelated with actual utility." *Id.* at 856.

On appeal the C.C.P.A. reversed, holding that the Board "erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may

not establish a specific therapeutic use." *Id.* (emphasis added). The Court stated that "practical utility" was characterized as a use of the claimed discovery in a manner which provides some immediate benefit to the public, establishing the rule that "[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public.... [W]e conclude that adequate proof of any such activity constitutes a showing of practical utility." *Id.* (emphasis added).

The Court rejected Bowler's argument that the BP and GC-SMS tests are inconclusive showings of pharmacological activity since confirmation by statistically significant means did not occur until after the critical date. The Court stated that "a rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." *Id.* (emphasis added). The Court concluded that a "reasonable correlation" between the observed properties and the suggested use was sufficient to establish practical utility. *Id.* at 857.

The test articulated in *Nelson* is certainly met by the evidence in Example 18. Presented with the data in Example 18, one of skill in the art would find that there is a "reasonable correlation" between the observed property of differential expression in certain tumors and the suggested use as a diagnostic tool for cancer. In *Nelson* the fact that the results were qualitative, not statistically significant, and preformed *in vivo* in rats or *in vitro* on gerbil colon did not matter. The Court held that statistically significant results are not required, nor is it necessary to prove actual clinical therapeutic usefulness.

The gene expression data in the specification, Example 18, shows that the mRNA associated with the PRO1268 polypeptide was more highly expressed in kidney tumor tissue compared to normal kidney tissue. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1268 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. Applicants previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

Thus, contrary to the PTO's position that "the increase in message was found in only one cancerous tissue" (See Office Action at 6), the use of pooled samples increases the accuracy of the experiment. As Dr. Grimaldi explained, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. Clinical diagnostics are geared towards generally relevant conditions that are present in a populous, such as a population of individuals with kidney tumors.

With respect to the PTO's concerns regarding the methodology used to compare mRNA levels in normal tissue to that in cancerous tissue in Example 18, Applicants maintain that this methodology is reliable. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr.

Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

In sum, the data in Example 18 are sufficient to establish a practical utility for the claimed invention. Applicants are asserting that the PRO1268 gene and polypeptide have utility as diagnostic tools for cancer, particularly lung cancer. Applicants are not asserting that the PRO1268 gene and polypeptide necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools, to assist in the diagnosis of kidney cancer. Statistically significant results are not required, nor is it necessary to prove actual clinical therapeutic usefulness.

The PTO cites Pennica *et al.* as teaching "a *lack* of correlation between DNA expression and increased peptide levels." Office Action at 3, emphasis in original. However, in contrast to the PTO's characterization of the reference, Pennica teaches nothing about a lack of correlation between the level of DNA expression and the level of protein expression – Pennica did not even look at protein expression. Since Pennica provides no data whatsoever regarding protein expression, nothing in Pennica can support the assertion that there is a lack of correlation between mRNA levels and increased peptide levels. Accordingly, nothing in Pennica is contrary to Applicants' assertion that it is established in the art that changes in the level of mRNA are correlated to the changes in the level of protein.

The PTO rejects the Grimaldi Declaration as insufficient to overcome the rejection of Claims 6-17. The PTO states that "the PRO1268 gene or mRNA has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1268 nucleic acid was increased in one cancer sample...it is not clear that the reported expression is meaningful." Office Action at 6, emphasis in original.

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating

to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *See in re Alton*, 76 F.3d 1168 (Fed. Cir. 1996).

While it is true that the specification provides only mRNA expression data, as Applicants explain in detail below, one of skill in the art would accept that increases or decreases in mRNA level for a particular gene are reasonably correlated with increases or decreases in the encoded polypeptide level, respectively. Therefore, there is a clear nexus between the differential expression of PRO1268 mRNA in kidney tumors and the differential expression of the PRO1268 polypeptide.

The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the nucleic acids of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

Applicants submit that a lack of known role for PRO1268 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. The PRO1268 gene can be used as a cancer diagnostic tool because it is differentially expressed in kidney tumors.

Applicants turn next to the PTO's arguments based on Hu *et al.* Applicants have discussed this reference at length in its previous responses. In addition to the persuasive reasons

articulated in Applicants' arguments of record, the PTO's reliance on Hu is also misplaced because Applicants are not relying on microarray data as discussed in Hu:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

Instead, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." Kuo *et al.* at Abstract (emphasis added) (attached as Exhibit 1). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1268 cDNA between kidney tumors and normal kidney tissue. Therefore, it follows that expression levels of the PRO1268 gene can be used to distinguish kidney tumor tissue from normal kidney tissue. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1268 polypeptide can also be used to distinguish kidney tumor from normal kidney tissue.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between Changes in mRNA Levels and Changes in the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1268 polypeptide in

kidney tumors, it is likely that the PRO1268 polypeptide is likewise differentially expressed in these tumors; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

The PTO's cited references are not contrary to Applicants' asserted utility

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis 1998; 19(11):1862-71) and Gygi *et al.* (Mol. and Cell. Bio., Mar. 1999; 1720-1730), as support for its argument that "mRNA levels are not predictive of protein levels." *Office Action* at 8. For the reasons discussed below, Applicants submit that the references cited by the PTO are either irrelevant, not contrary to Applicants' arguments, or actually offer support for Applicants' position.

Applicants have discussed at length in previous responses why the Haynes and Gygi references are not relevant to the issue of whether changes in mRNA level for a particular gene leads to changes in protein level. Applicants will not repeat their arguments here.

However, in an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to this issue, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes and Gygi discuss whether there is a correlation between the static level of mRNAs and proteins globally, *i.e.* across different genes. For example, in Experiment 1, if a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z, the ratio of the amount of proteins X:Y:Z would be 1:2:4, such that there is a correlation between static levels of mRNA and protein across genes. This is essentially what the cited references examined. In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein. For example, in Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the ratio of the amount of protein X in condition A:B would be 1:2, such that there is a correlation between the change in the level of mRNA and protein for a particular gene.

The PTO would like to argue that because there is no correlation between static levels of mRNA and protein across genes, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Example 2. This is simply wrong.

Applicants emphasize, and the PTO will recognize, that this is just a simplified illustration to demonstrate the difference between the two issues being examined. However, this illustration makes clear that even if there is no correlation in the first experiment looking at static levels across genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment.

The PTO's rejection of Applicants' asserted utility is based on a rejection of Applicants' conclusion that because the PRO1268 mRNA is differentially expressed in kidney tumors compared to normal kidney tissue, the PRO1268 polypeptide will be differentially expressed as well. This conclusion is not based on the assertion that steady-state mRNA levels are predictive of protein levels when comparing different genes, or that one can determine the level of mRNA based on changes in protein level. It is based on Applicants' assertion that changes in mRNA level generally result in corresponding changes in the level of the encoded protein. In rejecting this conclusion, the PTO has cited references by Pennica *et al.*, Hu *et al.*, Haynes *et al.*, and Gygi *et al.*

As explained previously, Pennica and Hu do not even discuss whether there is a correlation between mRNA and protein levels. While Haynes and Gygi address the relationship between mRNA and protein levels generally, their studies were limited to investigation of steady-state mRNA levels and correlations across different genes – a relationship which is irrelevant to Applicants' conclusion.

Taken as a whole, the references cited by the PTO do not support the PTO's rejection of Applicants' assertion that more often than not, there is a correlation between changes in mRNA level and changes in the level of the corresponding protein. If anything, the cited references support Applicants' position.

Applicants' previously submitted supporting declarations and references

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994), and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of these teachings, and how they support Applicants' asserted utility, are of record and will not be repeated here.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references referred to above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Finally, Applicants address the PTO's argument that "further research would have to be done to determine if PRO1268 mRNA and protein are amplified, and, if so, whether or not the expression is significant enough to reasonably confirm the usefulness of PRO1268 protein as a cancer marker." *See* Office Action at 7.

Applicants submit that a lack of known role for PRO1268 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO1268, for example, (see Office Action at 6) is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1268 is differentially expressed, or what the consequences of the differential expression are, in order to exploit the differential expression to distinguish tumor from normal tissue.

In fact, the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. The caveat in Example 12 states that the utility requirement is satisfied where a protein is expressed on melanoma cells but not on normal skin, and that antibodies against the protein can be used to diagnose cancer. The position of the PTO requiring a known role for PRO1268 in cancer for utility is also inconsistent with the analogous standard for therapeutic utility of a compound where "the mere identification

of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis in original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1268 mRNA is differentially expressed in kidney tumor tissue compared to normal kidney tissue, the PRO1268 polypeptide will also be differentially expressed in kidney tumor tissue compared to normal kidney tissue. This differential expression of PRO1268 and related polypeptides make them useful as diagnostic tools for cancer.

Applicants' additional supporting references

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 2), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin

and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further

understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good

correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Misrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at

Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 12) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed above, Applicants have challenged the relevance of references such as Haynes *et al.*, and Gygi *et al.*, which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 13) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a

"good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants' assertion in that they report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references in addition to the declarations and references already of record which support Applicants' asserted utility, either

directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 21). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1268 mRNA is differentially expressed in kidney tumor tissue, the PRO1268 polypeptide will likewise be differentially expressed in these tumors. This differential expression of the PRO1268 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly kidney tumor.

The Arguments made by the PTO are not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant**

> **provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by numerous references and the declarations of skilled experts.

Applicants' asserted utility is based on the assertion that changes in mRNA level generally result in corresponding changes in the level of the encoded protein. In rejecting this conclusion, the PTO has cited references by Pennica *et al.*, Hu *et al.*, Haynes *et al.*, and Gygi *et al.*

As explained above, these references are largely irrelevant when determining whether Applicants' asserted utility is more likely than not true. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence, including two uncontested expert declarations, excerpts from three textbooks, and over 115 scientific articles, is

more than sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly kidney tumor.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed PRO1268 polypeptides. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1268 gene and polypeptide in kidney tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1268 polypeptide is differentially expressed in kidney tumor tissue compared to normal kidney tissue. These data are strong evidence that the PRO1268 gene and polypeptide are associated with kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1268 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Applicants have addressed each of the PTO's supporting references and shown that they are either irrelevant, or taken as a whole, actually support Applicants' assertion that a change in mRNA level leads to a corresponding change in the level of the encoded protein. In addition, Applicants have submitted expert declarations, textbook excerpts, and over 115 scientific publications which support Applicants' asserted utility.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed PRO1268 polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 6-17 as lacking enablement. The PTO states that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants respectfully request that to the extent the enablement rejection is based on a lack of utility, the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 7, 2004

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